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Iridium−Monodentate Phosphoramidite-Catalyzed Asymmetric Hydrogenation of Substituted Benzophenone N−H Imines

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Chiral diarylmethylamines are found in numerous biologically active compounds of pharmaceutical relevance to human and animal health.[1] As a consequence, several approaches for their asymmetric synthesis have been devised.[2−6] Methodologies have relied upon stoichiometric, chiral-auxiliary-based additions of arylmetal reagents to *N*-aryl imines, oxazolidines, and *N*-*tert*-butanesulfinyl imines.[2] Significant improvements have been made recently with the development of rhodium-catalyzed enantioselective additions of arylstannane, aryltitanium, and arylboron reagents to *N*-sulfonyl, *N*-sulfamoyl, and *N*-*tert*-butanesulfinyl imines.[3] While these methods offer moderate to high stereocontrol, they also often involve use of excess reagents in their key steps as well as unproductive deprotection schemes to isolate the desired product amines.

Asymmetric hydrogenation of substituted benzophenone imines would provide a succinct, environmentally sound, and atom-economical approach to diarylmethylamines. Asymmetric hydrogenation of benzophenones to produce diarylmethanols has limited precedent,[7] and to the best of our knowledge, the corresponding asymmetric hydrogenations of benzophenone imines[8] are unknown. The obstacles encountered with the preparation and isolation of N-substituted benzophenone imines as single isomers have likely thwarted attempts involving their use as substrates in asymmetric hydrogenations.[9] We have recently reported on the enantioselective hydrogenation of N−H imines using iridium−*f*-binaphane as a catalyst system that provides efficient access to chiral amines without the requirement of nitrogen protection.[10] We present herein a concise, protection-free approach to the asymmetric synthesis of diarylmethylamines.

Benzophenone imines **1a**−**r** were synthesized in a single step on multigram scale, chromatography-free, via organometallic addition to benzonitriles.[11] Initial evaluations of 2-chlorobenzophenone imine substrate **1a** with $[Ir(COD)Cl]_2$ as the precatalyst and using chiral bidentate phosphines including *f*-binaphane, Segphos, Binap, and Josiphos (Scheme 1 and Table 1, entries 1−4) all gave low conversions to amine hydrochloride **2a** and moderate enantioselectivities at best. It is noteworthy that commercially available, inexpensive monodentate phosphoramidite ligands (Figure 1) gave superior results with improved conversion and enantioselectivities (entries 5−15).[12,13] (*S*,*S*,*S*)-MonoPhos PE (**3a**) gave slightly improved enantioselectivity over its corresponding (*S*,*R*,*R*) diastereomer **3b** (entries 11 and 12). Evaluation of amine substituent effects on the enantioselectivity led us to select (*S*)-*N*-benzyl-*N*-methyl-MonoPhos (**4**) as the ligand of choice for this hydrogenation (entries 11−15).[14] Increasing the H_2 pressure to 1500 psi ensured full conversion and maintained high enantioselectivity (entry 15). Examination of solvent effects revealed that a 3:1 CH_2Cl_2/MeOH combination afforded enantioselectivities of up to 87% ee (entries 13−15). Use of 1 mol % catalyst loading led to decreased reaction performance (28% conv, 77% ee).[15]

Scheme 1. Asymmetric Hydrogenation of 2-Chlorobenzophenone N−H Imine

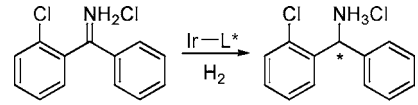
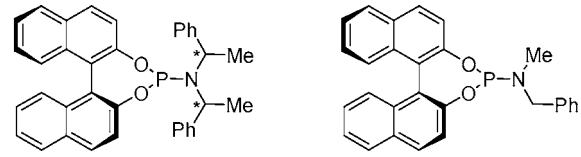


Table 1. Catalyst Evaluation for Asymmetric Hydrogenation of 2-Chlorobenzophenone N−H Imine **1a**[a]

entry	ligand	% conversion[b]	% ee[c]
1	(*S*,*S*)-*f*-binaphane	26	64
2	(*R*)-Segphos	25	64
3	(*R*)-Binap	47	64
4	Josiphos	12	52
5	(*S*)-SiPhos	99	62
6	(*R*,*R*,*R*)-SiPhos PE	20	20
7	(*R*)-MonoPhos	87	66
8	(*S*)-NEt_2-MonoPhos	70	80
9	(*S*)-MorPhos	85	76
10	(*S*)-PipPhos	62	83
11	(*S*,*R*,*R*)-MonoPhos PE	99	72
12	(*S*,*S*,*S*)-MonoPhos PE	99	80
13	(*S*)-*N*-Bn-*N*-Me-MonoPhos	99 (96)	83[d]
14	(*S*)-*N*-Bn-*N*-Me-MonoPhos	99	85[d,e]
15	(*S*)-*N*-Bn-*N*-Me-MonoPhos	99	87[d,f]

[a] Screening reaction conditions: $[Ir(COD)Cl]_2$/phosphine/substrate = 2.5:10:100, ligand/metal = 2:1, MeOH/CH_2Cl_2 = 2:1, 10 mg/mL, rt, 500 psi H_2, 36 h. [b] Determined by HPLC analysis; HPLC assay yield in parentheses. [c] Determined by chiral HPLC or SFC analysis of the corresponding acetamides (see the Supporting Information). [d] Reaction at 1500 psi. [e] CH_2Cl_2/MeOH = 2:1. [f] CH_2Cl_2/MeOH = 3:1.



(*S*,*S*,*S*)-MonoPhos PE **(3a)**
(*S*,*R*,*R*)-MonoPhos PE **(3b)**

(*S*)-*N*-Bn *N*-Me MonoPhos **(4)**

Figure 1

The effect of the counterion was evaluated using 2-chlorophenyl imine **1a**. Asymmetric hydrogenation of the corresponding imine·HBF_4 salt afforded decreased enantioselectivity (99% conv, 81% ee) relative to imine·HCl **1a** (Table 2, entry 1). Similarly, hydrogenation of the imine·HBF_4 salt under chloride-free conditions

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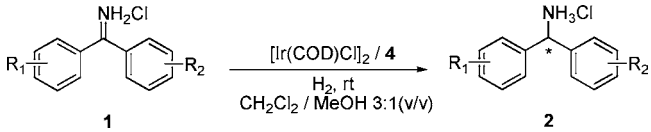
using cationic $Ir(COD)_2BF_4$ as the precatalyst resulted in poor performance (27% conv, 47% ee). The ability of the iridium−phosphoramidite catalyst system to perform under acidic reaction conditions and its tolerance to excess chloride ions is rather remarkable. In particular, the improved reaction outcome in the presence of chloride ion is somewhat counterintuitive since halide ions are known transition-metal-catalyst poisons.[9c,16]

Table 2. Asymmetric Hydrogenation of Substituted Benzophenone N−H Imines[a]



1 **2**

entry	R_1	R_2	**2**	yield (%)[b]	ee (%)[c,d]
1	2-Cl (**1a**)	H	**2a**	94	87
2	2-Br (**1b**)	H	**2b**	96	91
3	2-Me (**1c**)	H	**2c**	82	82 (*R*)
4	2-OMe (**1d**)	H	**2d**	88	76
5	2-F (**1e**)	H	**2e**	80	36
6	2-CF_3 (**1f**)	H	**2f**	95	98
7	3-Cl (**1g**)	H	**2g**	89	31
8	3-OMe (**1h**)	H	**2h**	93	46
9	4-Me (**1i**)	H	**2i**	96	31 (*S*)
10	2,3-Me_2 (**1j**)	H	**2j**	91	86
11	2-Cl (**1k**)	4-Me	**2k**	96	92
12	2-Cl (**1l**)	4-OMe	**2l**	93	93
13	2-Me (**1m**)	4-Me	**2m**	94	91
14	2-Me (**1n**)	4-OMe	**2n**	91	94
15	2-Cl-3-CF_3 (**1o**)	4-Me	**2o**	93	92
16	2,5-Cl_2 (**1p**)	4-Me	**2p**	90	72
17	2,6-Cl_2 (**1q**)	4-Me	**2q**	89	81
18	2-Me-5-Cl (**1r**)	4-OMe	**2r**	87	74

[a] Conditions: $[Ir(COD)Cl]_2$/ligand **4**/substrate = 2.5:10:100, 0.04 M, 1500 psi H_2, rt, 36 h. [b] Isolated yields. [c] Determined by chiral HPLC or SFC analysis of the corresponding acetamides (see the Supporting Information). [d] Absolute configuration determined by comparison with refs 3e and 10.

The hydrogenation appears to be sensitive to the steric and electronic nature of the substituent at the ortho position of the aromatic ring (Table 2). Chloro, bromo, and methyl substituents at the 2-position gave high enantioselectivities (82−91% ee; entries 1−3). Decreased reaction enantioselectivities were observed with coordinating 2-methoxy and smaller 2-fluoro substituents (entries 4 and 5). Asymmetric hydrogenation of 2-trifluoromethylbenzophenone imine **1f** gave up to 98% ee (entry 6). The increased enantioselectivity may be a consequence of the larger van der Waals hemispheric volume of a CF_3 group (42.6 Å^3) in comparison with a methyl group (16.8 Å^3).[17] Moving substituents to the meta position led to a significant decrease in enantioselectivity (entries 7−8). Similarly, a *p*-methyl substituent gave 31% ee (entry 9). A slight increase in enantioselectivity was observed when electron-donating 4-methyl or 4-methoxy groups were introduced as R_2 substituents (see entries 1, 11, and 12 and 3, 13, and 14, respectively). Benzophenone imines having more than one aromatic ring substituent gave enantioselectivities in the range 72−94% ee (entries 11−18).

In conclusion, we have developed an asymmetric hydrogenation of benzophenone N−H imines where ortho substitution is a key feature for high enantioselectivity. The reaction provides efficient access to diarylmethylamines without nitrogen protection. The highly modular and inexpensive nature of chiral phosphoramidite ligands coupled with the ease of preparation of N−H imines bodes well for further practical applications of this methodology.

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Supporting Information Available: Experimental procedures, characterization data for new compounds, and analysis of enantioselectivities of hydrogenation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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